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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,715	01/28/2002	Douglas William Hamilton	7250-12	8680

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,715	HAMILTON ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-47,64 and 65* is/are pending in the application.

4a) Of the above claim(s) *24,25,31-47 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,26-29 and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on September 13, 2004 has been received and entered. Claims 1-29, 31-47, 64 and 65 are pending.

Election/Restrictions

Applicants' election with traverse of Group I, claims 1-29 and 64, in the reply filed on September 13, 2004 is acknowledged. Applicants' election by telephone on October 7, 2004 of the species alginate for claim 8 and fibronectin for claim 28 is also acknowledged.

Claims 31-47 and 65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 24 and 25 are withdrawn from further consideration as being drawn to nonelected species.

In response to Applicants' remarks regarding unity of invention, the arguments have been considered. The amendments have been entered. Nevertheless, claims 24, 25, 31-47 and 65 remain withdrawn from prosecution as being drawn to non-elected inventions or species.

Regarding the restriction requirement, Applicants' comment that lack of unity of invention was not raised in the corresponding PCT application is noted. It is not mandatory, however, in a PCT application to restrict multiple inventions. An Examiner

may elect to examine multiple groups. Accordingly, unity of invention may be reassessed in the U.S. national phase application. PCT Rule 13 provides for restriction between multiple inventions, such as the compositions of Groups I-V and the methods of Groups VI-X.

Applicant is reminded that, for unity of invention to be found (in this case, among the first named composition, the first named method of making and the first named method of using), a special technical feature that defines the contribution that the invention makes over the prior art must be present in the originally presented claims in the first named invention. Thus, if a special technical feature is not found in Group I, unity of invention can no longer be found, and the claimed inventions may be restricted. Also, burden of search is not a criterion that applies in determining unity of invention, but the presence of a special technical feature, as discussed, and the number and statutory class of inventions claimed. Thus, the restriction requirement is deemed proper and is made final.

Claims 1-23, 26-29 and 64 are pending and are examined on the merits to the extent that they read on the elected species.

Claim Objections

Claims 14 and 22 are objected to because of the following informalities. Claim 14 recites "A substrate as claimed in claim 2wherein ... ." Claim 22 recites "A substrate as claimed in claim 19wherein ... ." The claims appear to contain typographical errors. If appropriate, Applicants may wish to amend the claims to recite, respectively "A

substrate as claimed in claim 2 wherein ..." and "A substrate as claimed in claim 19 wherein ... ."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, claim 15 recites an active agent and claim 17 recites a drug, growth factor or chemotactic agent. Although drugs, growth factors and chemotactic agents are types of active agents, no specific examples of an active agent, drug, growth factor or chemotactic agent are given. This claim language encompasses multitudes of possible compounds, including compounds neither contemplated nor disclosed by the specification as filed. Applicants have not provided any identification, description or structures for any active agent, drug, growth factor or chemotactic agent. Applicants have also not provided any guidance for identifying such compounds that function in the claimed invention to produce cell growth on the claimed substrate. In view of the great extent of the claimed subject matter, combined with the fact that the specification as filed provides no description of the

claimed compounds, it is clear that at the time of filing the application, Applicants possessed only cell growth substrates without an active agent. Thus, a holding of failure to meet the written description requirement is required.

Claims 15 and 17 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As discussed above with respect to the written description requirement, claim 15 recites an active agent and claim 17 recites a drug, growth factor or chemotactic agent, but no specific compounds are disclosed. As also discussed above, this claim language encompasses a multitude of possible compounds, including compounds neither contemplated nor disclosed by the specification as filed and for which Applicants have provided no guidance as to their structure or identity or as to methods for their selection or identification. In view of the great extent of the claimed subject matter, combined with the fact that the specification as filed provides a description of only cell growth substrates without an active agent, it is clear that in order to practice the scope of the claimed subject matter, the artisan of ordinary skill would have expected to have undertaken essentially a trial and error process to select or identify active agents that may function in the claimed invention. Such a process clearly amounts to undue experimentation. Because the specification provides no guidance as to the identity of compounds that may be used with the claimed cell growth

substrates, the skilled artisan clearly would have expected to have to experiment unduly to practice the claimed invention. In sum, undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth the claims (In re: Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A holding of non-enablement is, therefore, clearly required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites a substrate wherein the polysaccharide basal layer has a thickness greater than 60% of the thickness of this layer and the polysaccharide basal layer. Similarly, claim 4 recites a substrate wherein the polysaccharide basal layer has a thickness greater than 60% of the thickness of this layer and the polysaccharide basal layer. This claim language is confusing, and Applicants' intended meaning is not certain, rendering the claims indefinite. If appropriate, Applicants may amend the claims to recite a substrate wherein the polysaccharide basal layer has a thickness greater than 60% of the thickness of this layer and the cell adhesion protein layer (claim 3) and a substrate wherein the

polysaccharide basal layer has a thickness greater than 80% of the thickness of this layer and the cell adhesion protein layer (claim 4).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 64 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. This claim is drawn to the use of a substrate as claimed in claim 1 and is, therefore, unpatentable to Applicants because use claims do not correspond to a statutory class of subject matter as defined in 35 USC §101. It is suggested that Applicants use language such as "A method of culturing cells on a substrate, wherein the substrate comprises a polysaccharide and a cell adhesion protein ..." along with one or more method steps and the appropriate claim limitations to identify a method that would be statutory subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 9-23, 26-29 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmermann (EP 869173). Zimmermann discloses a substrate for growing cells that is made of porous alginate carriers. The substrate is coated with a cell adhesion protein, to which cells bind. The cell adhesion protein layer is adsorbed and non-covalently bound to the alginate layer, preferably by reacting the protein layer with a tannin solution, which creates hydrogen bonds between the carboxyl groups of the protein and the phenolic groups of the tannin. Cells can also grow in the pores of the alginate matrix. The alginate is composed of guluronic acid and mannuronic acid, preferably at a ratio of about 30%:70%, respectively. Cells can be removed from the surface layer by contacting the substrate with a solution of EDTA, which chelates the calcium in the alginate and cell adhesion layers. Loosening the substrate structure frees the cells from the surface. The substrate may also contain nutrients, growth factors, hormones or antibiotics to promote cell growth. See col. 1, line 48, to col. 2, line 26; col. 3, lines 11-35; col. 4, lines 12-23 and 51-58; and col. 5, lines 21-47. With regard to claims 9-13, although Zimmermann does not disclose the percentage of alginate in the alginate layer and the percentage of fibronectin in the fibronectin layer, because these compounds are not mixed with any other compound to form their respective layers, the percentages are 100% or close to 100%, allowing for impurities in the formation processes. As a result, the teachings of Zimmermann read on these claims. Thus, a holding of anticipation is required.

Claims 1-5, 9-19, 26-29 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Sefton et al. (WO 97/16176). Sefton discloses cell growth substrates that are microcapsules less than or equal to 500 μ in diameter. The microcapsules contain an immobilization matrix, such as an alginate matrix, an attachment matrix, such as fibronectin, and a bioactive compound, such as EGF, bFGF or NGF to promote cell growth. The substrates also contain cells attached to the attachment matrix. The substrates are coated with a permeable, hydrophilic polymer layer that promotes the exchange of nutrients, waste products and secreted cellular products between the cells of the microcapsules and the circulatory system of the animal into which the microspheres are placed (see pp. 20-22, in particular p. 21, 2^{d} full paragraph). As discussed above, regarding claims 9-13, although Sefton does not disclose the percentage of alginate in the alginate layer and the percentage of fibronectin in the fibronectin layer, because these compounds are not mixed with any other compound to form their respective layers, the percentages are 100% or close to 100%, allowing for impurities in the formation processes. As a result, the teachings of Sefton read on these claims. Thus, a holding of anticipation is required.

Claims 1-5, 7, 9-21, 26-29 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Brekke et al. (US 5,855,608). Brekke discloses a substrate for growing cells that is composed of alginate and coated with the RGD attachment moiety of fibronectin (the cell surface receptor binding domain) and that integrates cells from in vitro culture or from tissue and biologically active agents such as growth factors, drugs

and morphogenic agents (see col. 3, lines 1-10; col. 4, line 36, to col. 5, line 11, col. 6, lines 5-13; col. 12, lines 28-58). One alginate disclosed by Brekke is Keltone-HV (see col. 10, lines 50-55), which has a ratio of mannuronic acid (M):guluronic acid (G) of about 3:1, or about 75%:25% (see enclosed abstract of Siddiqui, Carbohydrate Research 67(1):289-293, 1978). Although the M:G ratio of Keltone-HV is not exactly the same as Applicants' ratio of 65:35, the two ratios are close, and Keltone-HV is merely one example of an alginate taught by Brekke. As discussed above, regarding claims 9-13, although Brekke does not disclose the percentage of alginate in the alginate layer and the percentage of fibronectin in the fibronectin layer, because these compounds are not mixed with any other compound to form their respective layers, the percentages are 100% or close to 100%, allowing for impurities in the formation processes. As a result, the teachings of Brekke read on these claims. Thus, a holding of anticipation is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23, 26-29 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann (EP 869173), Sefton et al. (WO 97/16176) and Brekke et al. (US 5,855,608). As discussed above with respect to claims 1-5, 7, 9-23, 26-29 and 64, Zimmermann discloses a substrate for growing cells that is made of porous alginate carriers. The substrate is coated with a cell adhesion protein, to which cells bind. The cell adhesion protein layer is adsorbed and non-covalently bound to the alginate layer, preferably by reacting the protein layer with a tannin solution, which creates hydrogen bonds between the carboxyl groups of the protein and the phenolic groups of the tannin. Cells can also grow in the pores of the alginate matrix. The alginate is composed of guluronic acid and mannuronic acid, preferably at a ratio of about 30%:70%, respectively. Cells can be removed from the surface layer by contacting the substrate with a solution of EDTA, which chelates the calcium in the alginate and cell adhesion layers. Loosening the substrate structure frees the cells from the surface. The substrate may also contain nutrients, growth factors, hormones or antibiotics to promote cell growth. See col. 1, line 48, to col. 2, line 26; col. 3, lines 11-35; col. 4, lines 12-23 and 51-58; and col. 5, lines 21-47.

Also as discussed above with respect to claims 1-5, 9-19, 26-29 and 64, Sefton discloses cell growth substrates that are microcapsules less than or equal to 500 μ in diameter. The microcapsules contain an immobilization matrix, such as an alginate matrix, an attachment matrix, such as fibronectin, and a bioactive compound, such as EGF, bFGF or NGF to promote cell growth. The substrates also contain cells attached to the attachment matrix. The substrates are coated with a permeable, hydrophilic polymer layer that promotes the exchange of nutrients, waste products and secreted cellular products between the cells of the microcapsules and the circulatory system of the animal into which the microspheres are placed (see pp. 20-22, in particular p. 21, 2^{d} full paragraph).

With respect to claims 1-5, 7, 9-21, 26-29 and 64, as discussed above, Brekke discloses a substrate for growing cells that is composed of alginate and coated with the RGD attachment moiety of fibronectin (the cell surface receptor binding domain) and that integrates cells from in vitro culture or from tissue and biologically active agents such as growth factors, drugs and morphogenic agents (see col. 3, lines 1-10; col. 4, line 36, to col. 5, line 11, col. 6, lines 5-13; col. 12, lines 28-58). One alginate disclosed by Brekke is Keltone-HV (see col. 10, lines 50-55), which has a ratio of mannuronic acid (M):guluronic acid (G) of about 3:1, or about 75%:25% (see enclosed abstract of Siddiqui, Carbohydrate Research 67(1):289-293, 1978). Although the M:G ratio of Keltone-HV is not exactly the same as Applicants' ratio of 65:35, the two ratios are close, and Keltone-HV is merely one example of an alginate taught by Brekke.

As mentioned above, regarding claims 9-13, although Zimmermann, Sefton and Brekke do not disclose the percentage of alginate in the alginate layer and the percentage of fibronectin in the fibronectin layer, because these compounds are not mixed with any other compound to form their respective layers, the percentages are 100% or close to 100%, allowing for impurities in the formation processes. As a result, the teachings of Zimmermann, Sefton and Brekke read on these claims.

Neither Zimmermann nor Sefton nor Brekke discloses a cell growth substrate in which the cell adhesion protein layer has a thickness of 1-20 μ or 3-5 molecules. The cited references differ from the claims in that they do not disclose the thickness of the cell adhesion protein layer recited in claims 6 or 8. As the layer thickness, however, is clearly a result-effective parameter routinely optimized by the artisan of ordinary skill at the time of Applicants' invention, the determination of suitable thicknesses for preparing a cell growth substrate, as recited in claims 6 and 8, clearly would have been a matter of routine optimization on the part of the artisan of ordinary skill and therefore obvious under § 103(a). Moreover, the choice of particular dimensions for the cell adhesion protein layer does not seem to be associated with any particular effect and consequently represents an arbitrary choice among equally likely alternatives as the layer may be 3 molecules thick or 20 μ thick. Thus, a holding of obviousness is required.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, with alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner
Art Unit 1651

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2004-10-14